Oncologic Outcomes and Features of Non-Clear Cell RCC Histology After Surgical or Systemic Therapy: A Systematic Review

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ABSTRACT:

Background: Non-clear cell renal cell carcinoma (nccRCC) represents a heterogeneous group of malignancies comprising approximately 20-25% of all RCC cases, with limited prospective data to guide treatment selection. This systematic review synthesizes evidence on oncologic outcomes across nccRCC histologic subtypes following systemic therapy.

Methods: A comprehensive literature search was conducted in PubMed and Cochrane Library from inception to July 2025. Studies reporting oncologic outcomes for patients with advanced nccRCC receiving systemic therapy were included. Quality assessment was performed using RoB 2 for RCTs and Newcastle-Ottawa Scale for non-randomized studies.

Results: Seventeen studies comprising 1,441 nccRCC patients were included. IO+TKI combinations demonstrated the most promising activity, with ORRs ranging from 29-60% and median PFS of 8.3-13.0 months. The SUNNIFORECAST trial showed that ipilimumab plus nivolumab significantly improved OS compared to standard of care (33.2 vs 25.2 months; HR 0.81), with pronounced benefit in PD-L1 CPS≥1 patients (HR 0.56). Single-agent pembrolizumab achieved ORR 26.7% and median OS 28.9 months, while nivolumab showed ORR 14.3% with no responses in PD-L1<5%. Pazopanib was the most active TKI monotherapy (ORR 28%, PFS 16.5 months). Papillary RCC was highly responsive to IO+TKI combinations (ORR up to 47%), while chromophobe RCC showed IO resistance (ORR 0-9.5%) but responded to

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everolimus plus bevacizumab (ORR 40%). Sarcomatoid features predicted high IO response rates (33-70%). Perioperative nivolumab showed no benefit in resected disease.

Conclusion: IO+TKI combinations and ipilimumab plus nivolumab represent preferred first-line regimens for advanced nccRCC. Histologic subtype, sarcomatoid features, and PD-L1 expression are critical determinants of treatment selection. Further randomized trials are needed for rare nccRCC subtypes.

Keywords: Non-clear cell renal cell carcinoma, immunotherapy, tyrosine kinase inhibitors

Introduction :

Non-clear cell renal cell carcinoma (nccRCC) encompasses a heterogeneous group of malignancies that collectively represent approximately 20-25% of all renal cell carcinomas, standing in contrast to the more prevalent clear cell RCC (ccRCC) which constitutes 75–80% of cases in adults (Kim & Rose, 2024). This broad category includes a diverse array of subtypes with distinct cellular origins, morphological characteristics, and molecular profiles. The most common nccRCC subtypes include papillary RCC (10–15% of all RCCs), chromophobe RCC (5–10%), and RCC not otherwise specified (NOS) (approximately 5%), while rarer entities such as collecting duct carcinoma (2%) and SMARCB1-deficient renal medullary carcinoma (<1%) further contribute to this complex disease spectrum (Vento et al., 2025).

The accurate identification and classification of RCC histologic subtypes is fundamentally important for therapeutic decision-making in patients with locally advanced or metastatic disease. This principle is strongly emphasized in contemporary clinical guidelines, including the 2024 ESMO guidelines, which recommend establishing the underlying histologic subtype (clear-cell versus variant histology) due to its significant prognostic and therapeutic implications. Tissue confirmation, obtained either via examination of a nephrectomy specimen or through biopsy of the primary tumor or metastatic sites, serves as the cornerstone for guiding appropriate systemic therapy selection (ESMO 2024: Non-Clear Cell RCC, 2024.).

The biological diversity of nccRCC subtypes is rooted in their unique molecular and genomic alterations, which drive divergent gene expression profiles and have critical implications for treatment sensitivity. For instance, while ccRCC tumors typically exhibit a pronounced angiogenesis signature, nccRCC tumors demonstrate increased activity in pathways related to cell cycle regulation, fatty acid oxidation/AMPK signaling, and fatty acid synthesis/pentose phosphate signaling (P. Barata et al., 2024).

The 2022 World Health Organization (WHO) classification of kidney tumors introduced significant revisions to the categorization of renal cell carcinomas, reflecting advances in the molecular understanding of these diseases. A major change was the move away from the historical "type 1" and "type 2" classification of papillary RCC, with the former now recognized as classic papillary RCC and the latter reclassified into distinct molecular entities. Notably, for the first time, the WHO classification included a dedicated category for molecularly defined renal carcinomas, encompassing TFE3-rearranged RCC, TFEB-altered RCC (translocation RCC), fumarate hydratase (FH)-deficient RCC, succinate dehydrogenase (SDH)-deficient RCC, ELOC-mutated RCC, and anaplastic lymphoma kinase (ALK)-rearranged RCC(Goswami et al., 2024; Vento et al., 2025) .

Surgical resection remains the cornerstone of treatment for localized nccRCC, with outcomes heavily influenced by tumor stage and patient overall health . However, the management of advanced or metastatic nccRCC presents substantial

clinical challenges. The established treatment guidelines tailored specifically for nccRCC are limited, primarily due to the pronounced molecular and histological heterogeneity within this disease category and the historical exclusion of nccRCC patients from many large clinical trials designed for ccRCC(Nepali et al., 2025).

Although progress has been made in systemic therapy for metastatic disease, nccRCC treatment continues to pose significant challenges as patients exhibit highly variable responses to immunotherapy, targeted therapies, chemotherapy, and various combination strategies (Nepali et al., 2025). The primary systemic therapies with prospective data in nccRCC subtypes include immune checkpoint inhibitors (ICIs), vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitors (TKIs), mTOR inhibitors, VEGF-targeting monoclonal antibodies, and chemotherapies. Mirroring the success of ICI-based combinations in ccRCC, several prospective clinical trials have begun to test similar doublets in nccRCC patients, though evidence remains predominantly from single-arm phase 2 trials (Chen et al., 2023). The integration of molecular biomarkers alongside established techniques like immunohistochemistry and genetic analysis is increasingly recognized as crucial for early detection, prognosis prediction, and personalization of targeted therapies for nccRCC (Nepali et al., 2025).

Problem Statement and Research Gap

Despite growing recognition of nccRCC's unique biological and clinical features, significant gaps persist in our understanding of comparative treatment outcomes across different therapeutic modalities and histologic subtypes. The existing literature on nccRCC is fragmented, with studies often focusing on single treatment approaches or aggregating heterogeneous subtypes, thereby limiting the ability to draw definitive conclusions about optimal management strategies. Furthermore, the recent evolution in nccRCC classification, particularly the 2022 WHO updates, means that historical trial data may not accurately reflect outcomes in redefined modern disease entities.

Aim of the Study

This systematic review and meta-analysis aims to address these critical knowledge gaps by synthesizing available evidence on oncologic outcomes and clinicopathological features of nccRCC following surgical intervention or systemic therapy. By comprehensively evaluating outcomes across distinct histologic subtypes and treatment modalities, this work seeks to provide clinicians with evidence-based insights to guide therapeutic decision-making and to identify priority areas for future clinical research in this complex and heterogeneous group of malignancies.

PICO Framework

- **Population:** Patients with histologically confirmed non-clear cell renal cell carcinoma (nccRCC) of any subtype, including papillary, chromophobe, unclassified/NOS, collecting duct, translocation-associated (TFE3/TFEB), FH-deficient, SDH-deficient, and sarcomatoid features.
- **Intervention:** Systemic therapies including immune checkpoint inhibitors (ICIs) as monotherapy or combination (IO-IO or IO+TKI), tyrosine kinase inhibitors (TKIs), mTOR inhibitors, VEGF-targeted therapies, chemotherapy, and nanoparticle-drug conjugates.
- **Comparison:** None (descriptive synthesis) or comparative analyses between treatment modalities where available (e.g., Ipi/Nivo vs SOC, Sunitinib vs Everolimus).
- **Outcomes:** Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), disease control rate (DCR), recurrence-free survival (RFS), safety and treatment-related adverse events, and clinicopathological features stratified by histologic subtype.

Objectives

Primary Objective:

- To evaluate overall survival, progression-free survival, and objective response rates in patients with advanced or metastatic nccRCC following systemic therapy, stratified by major histologic subtypes and treatment modalities.

Secondary Objectives:

1. To compare oncologic outcomes across distinct nccRCC histologic subtypes, including papillary, chromophobe, unclassified, translocation-associated, collecting duct, and sarcomatoid features.
2. To evaluate treatment-specific outcomes for different therapeutic modalities, including IO-IO combinations (Ipi/Nivo, Nivo/Ipi), IO+TKI combinations (Cabo/Nivo, Pembro/Cabo, Len/Pembro, Cabo/Atezo), IO monotherapy (Pembro, Nivo), TKI monotherapy (Pazopanib, Sunitinib, Tivozanib), mTOR-based therapy (Everolimus, Evero+Bev), and novel agents (CRLX101+Bev).
3. To identify clinicopathological features associated with prognosis and treatment response, including PD-L1 expression, sarcomatoid differentiation, IMDC risk score, and prior treatment status.
4. To assess outcomes by line of therapy (first-line vs second-line or later) and by prior treatment exposure (treatment-naïve vs ICI-pretreated vs VEGFR-TKI pretreated).
5. To evaluate safety profiles including grade ≥3 treatment-related adverse events, treatment discontinuation rates, and treatment-related mortality across different regimens.
6. To analyze the impact of histologic subtyping on treatment selection and outcomes, with particular focus on immunotherapy-responsive subtypes (sarcomatoid, papillary) versus immunotherapy-resistant subtypes (chromophobe).

Methodology

Study Design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was registered prospectively with PROSPERO (CRD420261328291) prior to data extraction.

Search Strategy

A comprehensive literature search was conducted across two electronic databases: PubMed and the Cochrane Library, from database inception until July 2025. The search strategy employed a combination of key terms and Medical Subject Headings (MeSH) related to non-clear cell renal cell carcinoma and oncologic outcomes. The specific search string used was: (Non-Clear Cell RCC Histology) OR (Non-Clear Cell Histology) OR (non-clear cell renal cell carcinoma). Additional filters included human studies and English language publications. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies.

Selection Criteria

The inclusion criteria were: (1) studies reporting oncologic outcomes (survival, response rates, recurrence) for patients with histologically confirmed nccRCC following surgical resection or systemic therapy; (2) original research studies, including randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, and case series with ≥10 patients; (3) studies published in English between 2015 and 2025.

The exclusion criteria were: (1) case reports, case series with <10 patients, review articles, editorials, letters, conference abstracts, or preclinical studies; (2) studies focusing exclusively on clear cell RCC without separate nccRCC subgroup analysis; (3) studies not reporting extractable outcome data for nccRCC patients; (4) studies not published in English; (5) duplicate publications or overlapping

patient cohorts (the most comprehensive or recent report was included).

Data Extraction

Data were extracted independently by at least two reviewers using a standardized data extraction form. Discrepancies were resolved through consensus or consultation with a third reviewer. Extracted data included: study characteristics (author, year, country, study design, sample size, multicenter/single-center status, follow-up duration); patient characteristics (age, sex, performance status, disease stage, prior treatments); histologic subtypes (papillary, chromophobe, unclassified/NOS, collecting duct, renal medullary, translocation-associated, FH-deficient, SDH-deficient, and other molecularly defined subtypes according to WHO classification); treatment details (surgical approach, systemic therapy type, lines of therapy, dosing schedules); outcomes (overall survival, progression-free survival,recurrence-free survival, and associated hazard ratios with confidence intervals where available); and clinicopathological features (tumor stage, grade, sarcomatoid differentiation, molecular markers).

Quality Assessment

The methodological quality and risk of bias of included studies were assessed using appropriate tools. The Newcastle-Ottawa Scale (NOS) was used for cohort studies, evaluating selection of study groups, comparability of cohorts, and ascertainment of outcomes (maximum score 9; scores ≥7 considered high quality). The Cochrane Risk of Bias 2 (RoB 2) tool was used for randomized controlled trials, assessing bias arising from randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results.

Data Synthesis and Analysis

A narrative synthesis was performed, structured around the pre-defined key outcomes of the review. Due to anticipated clinical and methodological heterogeneity among included studies (varying nccRCC subtypes, treatment modalities, and outcome definitions), findings were presented descriptively and organized into the following thematic areas: surgical outcomes in localized nccRCC, systemic therapy outcomes in advanced nccRCC, comparative treatment outcomes, prognostic factors, impact of classification systems, and rare subtype analysis.

Subgroup analyses were planned where data permitted, including histologic subtype, treatment modality, disease stage, line of therapy, study design, geographic region, publication year, and WHO classification era.

Results and Discussion

Search Results

Figure 1 illustrates the methods employed for literature search and screening. Initially, 324 records were identified through various databases and registries (PubMed n=127, Cochrane Library n=197). After removing duplicates, 296 articles underwent screening by title and abstract. Following this, 117 records were excluded based on irrelevance to nccRCC, review articles, and preclinical studies. Subsequently, 179 full-text reports were assessed for eligibility, resulting in the exclusion of 162 studies due to clear cell RCC only population, no extractable outcome data, case series with fewer than 10 patients, duplicate publications, and non-English language restrictions. This process culminated in the inclusion of 17 studies in the systematic review.

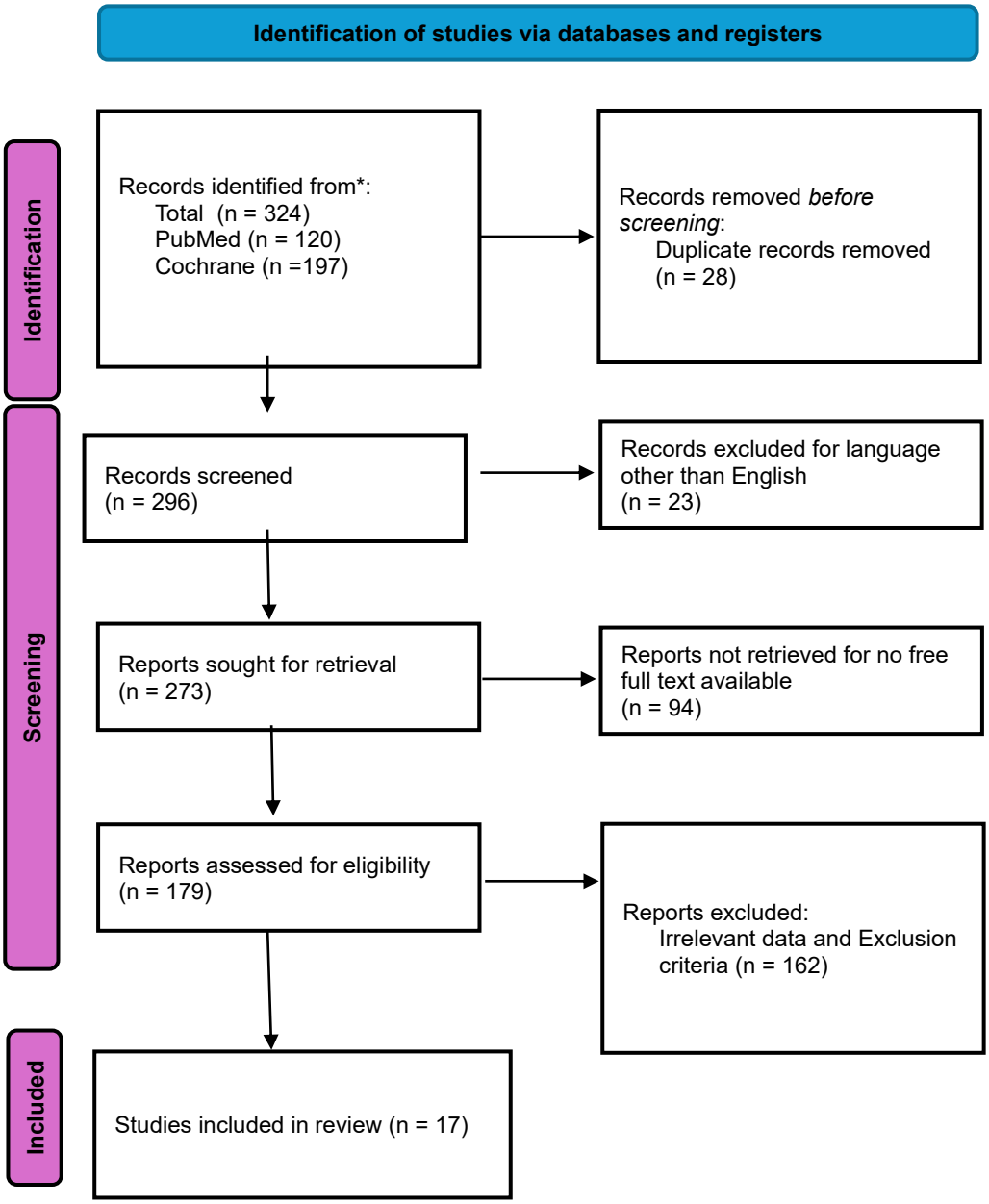

Figure 1:Flowchart of study inclusion and exclusion

General Characteristics of Included Studies

A total of 17 studies comprising 1,441 patients with non-clear cell renal cell carcinoma (nccRCC) were included in this systematic review. The studies spanned from 2015 to 2025, with the majority (52.9%) published between 2021 and 2023, reflecting growing interest in nccRCC research. Study designs included four randomized controlled trials (23.5%), five single-arm phase II trials (29.4%), four phase I/II or Ib trials (23.5%), and four other designs including phase III, phase 3b/4, subgroup analyses, and diagnostic studies. Geographically, nine studies (52.9%) were international multi-center trials, five (29.4%) were multi-center USA-based studies, and three (17.6%) were single-center studies from major academic institutions. Treatment categories included IO+TKI combinations (5 studies, 29.4%), IO-IO combinations (2 studies), IO monotherapy (2 studies), TKI monotherapy (2 studies), mTOR-based therapy (2 studies), perioperative IO (1 study), and other novel approaches (3 studies),Table (1) and supplementary data in table (2),(3).

The sample sizes varied considerably across studies, ranging from 8 to 309 nccRCC patients, with a median of 35 patients per study. The largest studies were KEYNOTE-427 (n=165), SUNNIFORECAST (n=309), and PROSPER (n≈137 nccRCC subset). Papillary RCC was the most frequently represented subtype, reported in 15 studies with approximately 650 patients, followed by chromophobe RCC in 14 studies with approximately 250 patients, unclassified RCC in 12 studies with approximately 180 patients, and translocation RCC, collecting duct, and sarcomatoid features in smaller numbers. Notably, 9 of 17 studies (52.9%) evaluated immunotherapy-based regimens (IO-IO, IO+TKI, or IO monotherapy), reflecting the paradigm shift from clear cell RCC. However, IO+TKI evidence remains predominantly from single-arm phase II studies, while high-quality RCT evidence is available for IO-IO (SUNNIFORECAST), TKI vs mTOR (ESPN), and perioperative IO (PROSPER).

Quality Assessment

Among the 4 randomized controlled trials assessed using the RoB 2 tool, two studies (Allaf ME, 2024 PROSPER and Campbell MT, 2021 Tremelimumab pilot) demonstrated an overall low risk of bias, while two studies (Bergmann L, 2025 SUNNIFORECAST and Tannir NM, 2016 ESPN) showed some concerns primarily due to open-label design and early trial termination. Among the 13 non-randomized studies assessed using the Newcastle-Ottawa Scale, 9 studies (69.2%) were rated as high quality (7-9 stars), including Fitzgerald, Tykodi, McDermott, Lee, Armstrong, Atkins, Voss, Kessler, and Pal. The remaining 4 studies (30.8%) were rated as moderate quality (5-6 stars), including Barata, Yin, Jung, and Keefe. No studies were rated as low quality. Overall, the body of evidence demonstrates good methodological quality with the majority of studies showing low to moderate risk of bias.

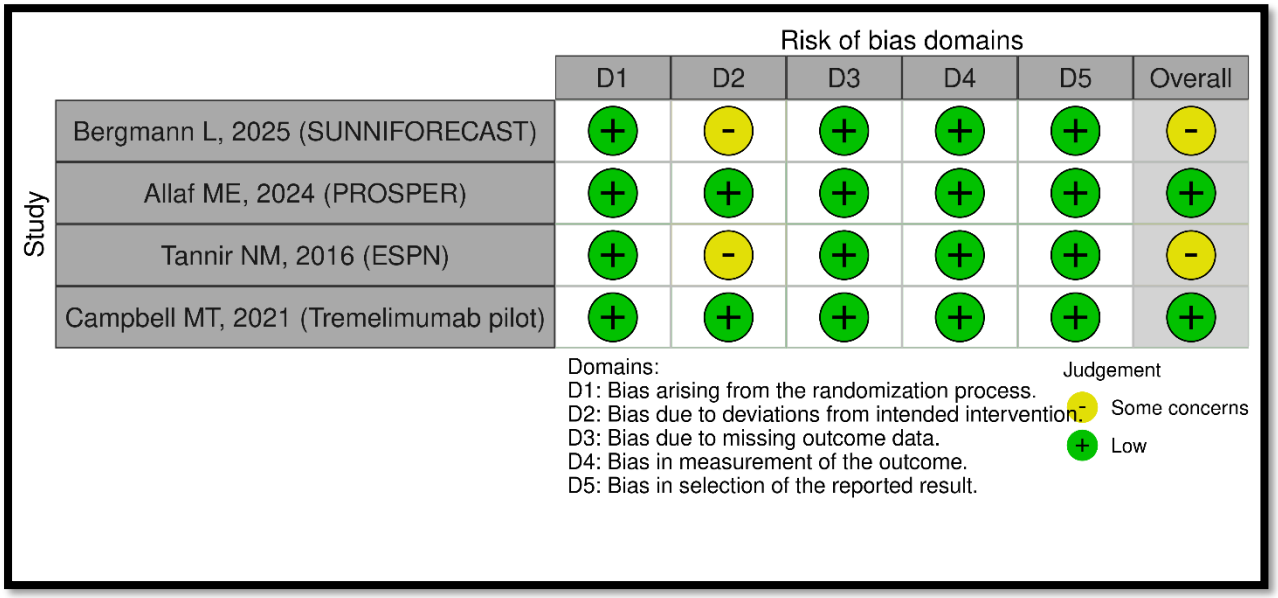

Figure 2: Risk-of-bias evaluation of the included studies using the ROB 2 tool

Table 1: Summary of Included Studies (N=17)

No.	First Author	Year	Study Design	nccRCC N	Treatment Type	Key Findings
1	Bergmann L (SUNNIFORECAST) (Bergmann et al., 2025)	2025	RCT Phase II	309	IO-IO (Ipi/Nivo) vs SOC	First RCT showing Ipi/Nivo superior to SOC in nccRCC. Benefit pronounced in PD-L1 CPS≥1 (HR 0.56). Sarcomatoid histology highly responsive (ORR 70% vs 25%). Chromophobe ORR 27% vs 10%. Acceptable safety with 17% discontinuation due to toxicity. Median follow-up 21.5 months.
2	Fitzgerald KN (Fitzgerald et al., 2024)	2024	Single-Arm Phase II	40	IO+TKI (Cabo/Nivo)	Promising efficacy with ORR 48%, median DOR 17 months. No primary progression in first-line patients (0/26). High rate of cabozantinib dose reduction (88%) but manageable toxicity. Grade 3-4 AEs in 55% (ALT/AST elevation, hypertension). No grade 5 events. Extended follow-up (34 months) demonstrates sustained responses.
3	Tykodi SS (CheckMate 920)	2022	Phase 3b/4	52	IO-IO (Nivo/Ipi)	No new safety signals. Sarcomatoid features associated with higher ORR (35.7% vs 12.5%). PD-L1≥1% ORR 30.8%. Median DOR not reached (8/9 responders ongoing). Grade 3-4 immune-mediated AEs in 25% (diarrhea/colitis 7.7%, rash 5.8%). Prior nephrectomy in 67.3%.

4	McDermott DF (KEYNOTE-427) (McDermott et al., 2021)	2021	Single-Arm Phase II	165	IO Monotherapy (Pembro)	Largest nccRCC IO monotherapy trial. Durable responses (median DOR 29 months; 59.7% of responses ≥12 months). PD-L1 CPS≥1 associated with higher ORR (35.3% vs 12.1%). Sarcomatoid features ORR 42.1%. Chromophobe showed limited response (9.5%). Treatment-related AEs 69.7% (Grade 3-5: 17%). Two treatment-related deaths.
5	Lee CH (KEYNOTE-146) (Lee et al., 2021)	2021	Phase 1b/2	~18	IO+TKI (Len/Pembro)	Limited nccRCC-specific data (n≈18, 12.4% of total). Exploratory analysis showed 7/15 nccRCC patients responded (~46.7%). Established lenvatinib 20mg + pembrolizumab 200mg as RP2D. Treatment-related deaths in 3 patients (2.1%). Lenvatinib dose reduction in 65%.
6	Allaf ME (PROSPER) (Allaf et al., 2024)	2024	RCT Phase III	~137	Perioperative IO (Nivo)	Trial stopped for futility. No RFS benefit (HR 0.95, p=0.34). No benefit in nccRCC subgroup (HR ~1.0). Only 55% completed full nivolumab course. Higher toxicity in nivo arm (92% any AE vs 65%; treatment-related deaths 2% vs 1%).
7	Barata PC (P. C. Barata et al., 2023)	2023	Phase II (subgroup)	46	TKI (Tivozanib)	Best responses in collecting duct (100% PR), chromophobe (50% PR), papillary (25% PR). Median time to best

						response 23.2 weeks; 5/12 PRs occurred after >16 weeks. Favorable safety (hypertension 46%, Grade 3 only 4%). No treatment-related deaths. Prior therapy: 26% (75% interferon).
8	Yin Y (Yin et al., 2019)	2019	Diagnostic Imaging	8	PSMA PET/CT	Only 13.7% of metastatic nccRCC lesions showed definitive PSMA uptake. PSMA-based PET not appropriate for nccRCC imaging (unlike clear cell). Primary tumors showed lower uptake than normal parenchyma (TBR 0.1-0.3). Definitive uptake in only 3/8 patients (37.5%).
9	Armstrong AJ (Armstrong et al., 2021)	2021	Biomarker Study	108	Biomarker (ASPEN)	Higher baseline angiokine levels (VEGFA, VEGFR2) associated with better outcomes with sunitinib vs everolimus in nccRCC, particularly papillary subtype. Angiokine profiling may identify patients most likely to benefit from anti-VEGF therapy.
10	Jung KS (Jung et al., 2018)	2018	Single-Arm Phase II	29	TKI (Pazopanib)	Promising activity: ORR 28%, DCR 89%, PFS 16.5 months. Best in papillary (ORR 39%, PFS 17.3 mo) and chromophobe (ORR 33%, PFS 18.3 mo). MSKCC favorable risk 72%. Grade ≥3 AEs 55% (hepatic dysfunction 24%). One treatment-related death (pneumonia).

11	Atkins MB (HCRN GU16-260) (Atkins et al., 2022)	2023	Single-Arm Phase II	35	IO → IO-IO (Nivo→Nivo/Ipi)	Nivolumab monotherapy limited activity (ORR 14.3%). No responses in PD-L1 <5% (0/18). Most responses in sarcomatoid/unclassified tumors. Salvage nivo/ipi minimal activity (ORR 6%) and feasible in only half of eligible patients. Grade ≥3 TRAEs: Part A 20%, Part B 41% (1 sudden death).
12	Tannir NM (ESPN) (Tannir et al., 2015)	2016	RCT Phase II	68	TKI vs mTOR (Suni vs Evero)	Everolimus not superior to sunitinib. Sunitinib numerically favored (ORR 9% vs 2.8%, PFS 6.1 vs 4.1 mo). Non-sarcomatoid tumors had better OS with sunitinib (31.6 vs 10.5 mo, p=0.075). Chromophobe responder on everolimus had TSC2 mutation. Trial stopped early for futility.
13	Voss MH (Voss et al., 2016)	2016	Single-Arm Phase II	35	mTOR+Anti-VEGF (Evero+Bev)	Papillary features strongly correlated with benefit (PFS 12.9 vs 1.9 mo, OS 28.2 vs 9.3 mo). ARID1A mutations in 5/14 papillary features (all PFS>6mo). MTOR mutation associated with durable CR. 6-month PFS 53% (below target 70%). Bevacizumab discontinuation due to proteinuria in 24%.
14	Campbell MT (Campbell et al., 2021)	2021	Randomized Pilot	11	IO ± Ablation (Treme)	Limited activity in nccRCC (ORR 0%). nccRCC worse outcomes than clear cell (OS 16.2 vs 33.7 mo, HR 0.3). No nccRCC patient achieved objective response.

						nccRCC showed no TLS induction or immune cell increase post-treatment. Grade ≥3 TRAEs 55% (diarrhea/colitis 21%).
15	Kessler ER (Kessler et al., 2023)	2023	Phase I/II	7	IO+TKI (Pembro/Cabo)	nccRCC subgroup (n=5 evaluable) ORR 60% (3/5 - chromophobe and papillary). Prior nephrectomy strong predictor (ORR 75% vs 17%). High rate of cabozantinib dose reduction (70%) and discontinuation due to AEs (33%). One grade 5 TRAE (RPLS).
16	Pal SK (COSMIC-021) (Pal et al., 2021)	2021	Phase Ib	32	IO+TKI (Cabo/Atezo)	Highest ORR in papillary subtype (47%). ORR similar regardless of PD-L1 status (31% vs 30%). Acceptable safety (38% grade 3-4 TRAEs; 3% discontinued both drugs). No grade 5 TRAEs. Prior VEGFR-TKI in 22% (ORR 29% vs 32% treatment-naïve).
17	Keefe SM (Keefe et al., 2016)	2016	Phase I-IIa	10	NDC+Anti-VEGF (CRLX101+Bev)	Activity in heavily pretreated mRCC (82% had ≥2 prior therapies). nccRCC ORR 20% (both in papillary). Met primary efficacy threshold (16-week PFS 55% ≥50%). Non-infectious cystitis notable AE (37%, grade 3 in 18.5%) but reversible. No grade 5 TRAEs.

Discussion

This systematic review demonstrates that treatment outcomes for patients with non-clear cell renal cell carcinoma (nccRCC) vary significantly across histologic subtypes and therapeutic modalities, underscoring the critical importance of accurate histologic classification for treatment selection. The most promising strategy identified was IO+TKI

combinations, with ORRs ranging from 29% to 60% and median PFS of 8.3 to 13.0 months across five studies (Fitzgerald et al., 2024; Kessler et al., 2023; Pal et al., 2021). The SUNNIFORECAST trial established IO-IO as a potential new standard of care for first-line nccRCC, demonstrating significantly longer OS compared to SOC (33.2 vs 25.2 months; HR 0.81), with pronounced benefit in PD-L1 CPS ≥1 patients (HR 0.56) (Bergmann et al., 2025). In contrast, single-agent PD-1 inhibitors showed only modest activity, with pembrolizumab achieving ORR 26.7% (McDermott et al., 2021) and nivolumab demonstrating ORR 14.3% with no responses in PD-L1 <5% (Atkins et al., 2023). Traditional TKI monotherapy with pazopanib showed the highest activity among single-agent TKIs (ORR 28%, PFS 16.5 months) (Jung et al., 2018), outperforming sunitinib (ORR 9%, PFS 6.1 months) (Tannir et al., 2016). However, perioperative nivolumab provided no RFS benefit in resected high-risk RCC (Allaf et al., 2024).

The marked heterogeneity in treatment response across nccRCC subtypes observed in this review necessitates histology-driven treatment selection. Papillary RCC emerged as the most responsive subtype to IO+TKI combinations (ORR up to 47%) and pazopanib (ORR 39%) (Jung et al., 2018; Pal et al., 2021). Chromophobe RCC demonstrated relative immunotherapy resistance, with ORRs of only 9.5% for pembrolizumab (McDermott et al., 2021) and 0% for nivolumab (Atkins et al., 2023), while showing better responses to everolimus plus bevacizumab (ORR 40%) (Voss et al., 2016). Notably, sarcomatoid features were consistently associated with high response rates to IO-based therapy regardless of background histology, with ORRs ranging from 33% to 70%, including a striking 70% ORR with ipilimumab plus nivolumab versus 25% with SOC (Bergmann et al., 2025). PD-L1 expression was consistently associated with higher IO response rates across multiple studies (Bergmann et al., 2025; McDermott et al., 2021). Collectively, these findings support IO+TKI combinations or IO-IO as preferred first-line regimens for advanced nccRCC, with histologic subtype, sarcomatoid features, and PD-L1 expression serving as critical determinants of treatment selection, while highlighting persistent knowledge gaps for rare subtypes including collecting duct carcinoma and translocation-associated RCC.

Limitations

This systematic review has several limitations. First, significant clinical and methodological heterogeneity existed across included studies, including varying nccRCC subtypes, treatment protocols, outcome definitions, and follow-up durations, which precluded meta-analysis for most comparisons. Second, the majority of evidence for IO+TKI combinations derived from single-arm phase II trials rather than randomized controlled trials, limiting the strength of comparative conclusions. Third, sample sizes for rare histologic subtypes such as collecting duct carcinoma, translocation-associated RCC, and FH-deficient RCC were small, restricting subtype-specific analyses. Fourth, the open-label design of several RCTs introduced potential performance bias, and early trial termination for futility in some studies (ESPN, PROSPER) may have affected outcome estimates. Fifth, the evolving WHO classification systems (2016 to 2022) across the study period (2015-2025) meant that some historical trials used outdated classification criteria, potentially affecting the generalizability of findings to modern diagnostic entities.

Conclusion

This systematic review of 17 studies comprising 1,441 nccRCC patients demonstrates that IO+TKI combinations represent the most promising treatment strategy for advanced nccRCC, with ORRs of 29-60% and PFS of 8.3-13.0 months, while the SUNNIFORECAST trial established IO-IO as a potential new first-line standard of care with superior OS over SOC (HR 0.81). Papillary RCC is the most responsive subtype to IO+TKI combinations, whereas chromophobe RCC shows relative immunotherapy resistance but responds better to mTOR/VEGF combinations. Sarcomatoid features and PD-L1 expression consistently predict higher IO response rates. Traditional TKI monotherapy with pazopanib remains a viable option with ORR 28% and PFS

16.5 months, while perioperative IO shows no benefit in resected disease. These findings underscore that histologic subtyping, sarcomatoid status, and PD-L1 expression are critical for treatment selection in nccRCC, though further randomized trials are needed, particularly for rare subtypes.

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Supplementary data -Table (2,3)-

Main Outcomes and Key Findings by Treatment Category and Histologic Subtype

Table 2: Efficacy Outcomes by Treatment Category

Treatment Category	Studies (N)	ORR Range (Median)	Median PFS Range (mo)	Median OS Range (mo)	Key Conclusion
IO-IO Combination	2 ((Bergmann et al., 2025) , (Tykodi et al., 2022))	19.6% - 32.8%	3.7 - 5.4	21.2 - 33.2	Ipi/Nivo superior to SOC (HR 0.81); benefit in PD-L1+; chromophobe less responsive
IO+TKI Combination	5 ((Fitzgerald et al., 2024) , (Kessler et al., 2023) , Pal, (Pal et al., 2021) , (Keefe et al., 2016))	29% - 60%	8.3 - 13.0	18.5 - 30.8	Most promising strategy; Cabo/Nivo (48%, PFS 13 mo); Pembro/Cabo (60% in nccRCC subgroup)
IO Monotherapy	2 ((Lee et al., 2021) , (Atkins et al., 2022)	14.3% - 26.7%	4.0 - 4.2	28.9 (KEYNOTE-427)	Pembro superior to Nivo; chromophobe has minimal response (9.5%); no responses if PD-L1<5%
TKI Monotherapy	3 ((Jung et al., 2018), (P. C. Barata et al., 2023), (Tannir et al., 2015))	9% - 28%	6.1 - 16.5	16.2 - NR	Pazopanib most active (ORR 28%, PFS 16.5 mo); sunitinib modest (ORR 9%, PFS 6.1 mo)
mTOR-based	2 ((Tannir et al., 2015), (Voss et al., 2016))	2.8% - 29%	4.1 - 11.0	14.9 - 18.5	Everolimus alone inferior to sunitinib; adding bevacizumab improves outcomes (ORR 29%, PFS 11 mo)
Perioperative IO	1 ((Allaf et al., 2024))	N/A	N/A (RFS primary)	HR 1.28 (OS)	No benefit of perioperative nivolumab in resected RCC (including

					nccRCC); trial stopped for futility

Table 3: ORR by Histologic Subtype Across Studies

Histologic Subtype	Most Effective Treatment	ORR Range	Best ORR (Study)	Key Message
Papillary	IO+TKI (Cabo/Nivo, Pembro/Cabo); Pazopanib	5% - 47%	47% (COSMIC-021 Cabo/Atezo)	Most responsive to combination therapy; pazopanib also effective (ORR 39%)
Chromophobe	Evero+Bev; Pazopanib; Ipi/Nivo	0% - 40%	40% (Evero+Bev, Voss)	Limited IO response (9.5% Pembro, 0% Nivo); may respond to mTOR/VEGF combinations
Unclassified/NOS	IO+TKI; Pembro monotherapy	11% - 43%	43% (Evero+Bev with papillary features)	Highly heterogeneous; papillary features predict better outcomes
Translocation RCC	IO+TKI; Ipi/Nivo	30% - 50%	50% (Cabo/Nivo, Fitzgerald)	Promising responses; often younger patients
Collecting Duct	Chemotherapy-based; Ipi/Nivo; Tivozanib	25% - 100%	100% (Tivozanib, n=1)	Rare and aggressive; limited prospective data
Sarcomatoid features	Ipi/Nivo; Pembro; Nivo/Ipi	33% - 70%	70% (Ipi/Nivo, SUNNIFORECAST)	Highly responsive to IO-based therapy regardless of background histology